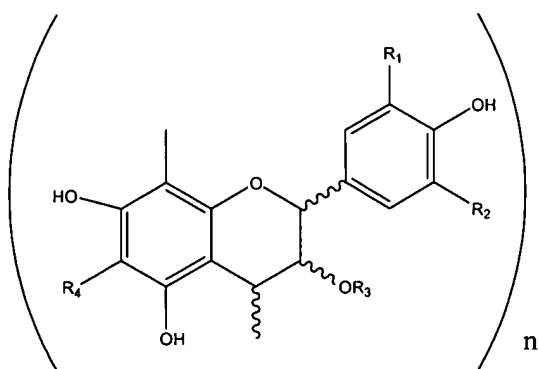


Amendments to the Claims:

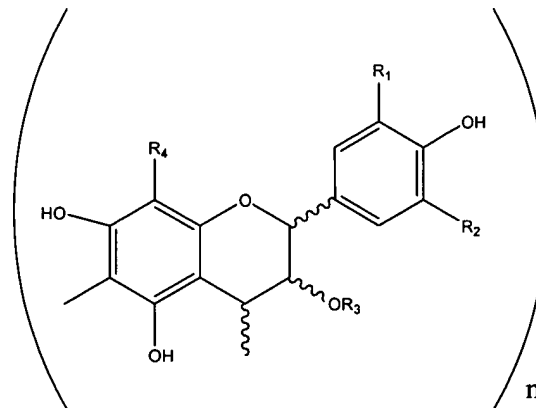
This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Withdrawn) A method of treating an amyloid disease, or a disease characterized by  $\alpha$ -synuclein or NAC fibrillogenesis, in a mammalian subject, the method comprising administering to the mammal a therapeutically effective amount of a proanthocyanidin, selected from the group of the proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins:



Formula I



Formula II

where:

n is an interger of 2 to 20;

R1 and R2 are independently selected from hydrogen and hydroxy;

R3 is selected from the group consisting of hydrogen, optionally substituted O-glycosyl, -C(O)-(optionally substituted aryl), and BC(O)-(optionally substituted heteroaryl);

R4 is selected from the group consisting of hydrogen, catechin, epicatechin, epiafzelechin, and gallates of catechin and epicatechin;  
the lines at the 2-, 3- and 4-position denote optional R and S configurations;  
the lines at the 4- and 8-positions in Formula I and at the 4- and 6- positions in Formula II denote possible oligomer bonds between individual units, and  
the substitutions at R1, R2, R3, and R4, and the configurations at the 2-, 3-, and 4-positions, and the oligomer bond configurations of 4-8 and 4-6 are independently selected for each individual unit.

2. (Withdrawn) The method of claim 1 where the proanthocyanidin is characterized by Formula I.

3. (Withdrawn) The method of claim 1 where the proanthocyanidin is characterized by Formula II.

4. (Withdrawn) The method of claim 1 where n is an interger of 2 through 5.

5. (Withdrawn) The method of claim 1 where the chiral configuration at each 2-position is R.

6. (Withdrawn) The method of claim 1 where each R3 is selected from hydrogen, 2,3-dihydroxybenzoyl, 3,4-dihydroxybenzoyl; 2,3,4-trihydroxybenzoyl, and 3,4,5-trihydroxybenzoyl.

7. (Withdrawn) The method of claim 2 where n is 2 or 3.

8. (Withdrawn) The method of claim 7 where each R3 is hydrogen.

9. (Withdrawn) The method of claim 8 where each R1 is hydroxy and each R2 is hydrogen.

10. (Withdrawn) The method of claim 1 where each R3 is optionally substituted O-glycosyl.

11. (Withdrawn) A method of treatment of an amyloid disease, or a disease characterized by  $\alpha$  -synuclein or NAC fibrillogenesis, in a mammalian subject, the method comprising the step of administering to the subject a therapeutically effective amount of a proanthocyanidin.

12. (Withdrawn) The method of claim 11, wherein the therapeutically effective amount of proanthocyanidin is a procyanidin oligomer having from 2 to 20 units.

13. (Withdrawn) The method of claim 12 in which the oligomer units are in the general form of flavanoid units and the procyanidin oligomer contains 2 to 5 units.

14. (Withdrawn) The method of claim 13 in which each flavanoid unit is selected from the group consisting of catechins, including catechin, epicatechin, epiafzelechin, gallocatechin, galloepicatechin, epigallocatechin and the gallates of the catechins, and flavanols, flavonols, flavandiols, leucocyanidins, and anthocyanidins.

15. (Withdrawn) The method of claim 1 where the amyloid disease is selected from the group of diseases consisting of Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, inclusion body myositis, the amyloidosis of chronic inflammation, the amyloidosis of malignancy and Familial Mediterranean Fever, the amyloidosis of multiple myeloma and B-cell dyscrasia, the amyloidosis of type 2 diabetes, the amyloidosis of prion diseases, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, scrapie, mad cow disease, the amyloidosis associated with long-term hemodialysis, the amyloidosis with carpal tunnel syndrome, senile cardiac amyloidosis, Familial Amyloidotic Polyneuropathy, the amyloidosis associated with endocrine tumors, systemic AA amyloidosis, AL amyloidosis, A $\beta$  amyloidosis and PrP amyloidosis.

16. (Withdrawn) The method of claim 15 where the amyloid disease is Alzheimer's disease.

17. (Withdrawn) The method of claim 1 where the  $\alpha$ -synuclein or NAC fibrillogenesis is a fibrillogenesis selected from the group consisting of Lewy body disease, Parkinson's disease and multiple system atrophy.

18. (Withdrawn) A method of treatment of amyloid,  $\alpha$ -synuclein or NAC fibrillogenesis, in an in vitro environment, the method comprising the step of administering into the in vitro environment a therapeutically effective amount of a proanthocyanidin.

19. (Withdrawn) The method of claim 14 wherein the procyanidin comprises an oligomer of epicatechin and/or catechin units, epiafzelechin and/or epicatechin units, and/or epicatechin gallates and/or catechin gallates.

20. (Withdrawn) The method of claim 19 wherein the procyanidin is a procyanidin selected from the group consisting of A, B and C type procyanidins.

21. (Withdrawn) The method of claim 20 wherein the procyanidin is a dimer or trimer of epicatechin and/or catechin units.

22. (Withdrawn) The method of claim 21 wherein the procyanidin is a dimer and is selected from the group consisting of type B1, B2, B3, B4, B5, B6, B7, and B8 type procyanidins.

23. (Withdrawn) The method of claim 22 wherein the procyanidin dimer is epicatechin-4 $\beta$ →8-epicatechin.

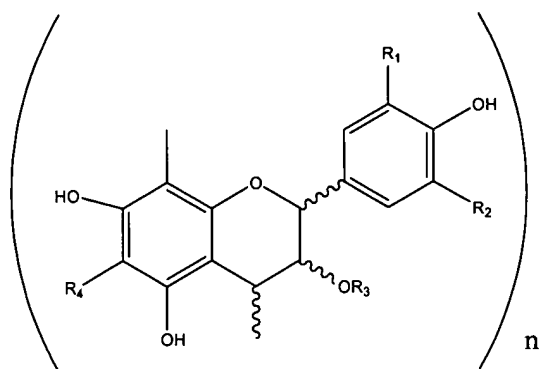
24. (Withdrawn) The method of claim 22 wherein the procyanidin dimer is catechin-4 $\alpha$ →8-epicatechin.

25. (Withdrawn) The method of claim 22 wherein the procyanidin dimer is epiafzelechin-4 $\beta$ →8-epicatechin.

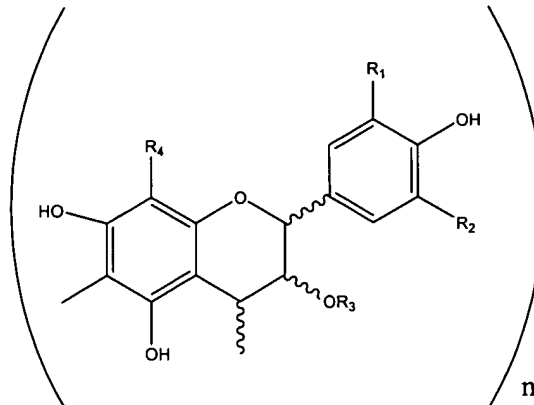
26. (Withdrawn) The method of claim 21 wherein the procyanidin is an epicatechin trimer, epicatechin-4 $\beta$ →8-epicatechin-4 $\beta$ →8-epicatechin.

27. (Withdrawn) The method of claim 11 further comprising an administration step whereby, the therapeutic amount of proanthocyanidin is administered to the subject, selected from the group of administration steps consisting of oral administration, parenteral injection, intraperitoneal injection, intravenous injection, subcutaneous injection, intramuscular injection, topical administration, and aerosol spray administration.

28. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins:



Formula I



Formula II

where:

n is an integer of 2 to 20;

R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen and hydroxy;

R<sub>3</sub> is selected from the group consisting of hydrogen, optionally substituted O-glycosyl,

-C(O)-(optionally substituted aryl), and BC(O)-(optionally substituted heteroaryl);

R<sub>4</sub> is selected from the group consisting of hydrogen, catechin, epicatechin, epiafzelechin, and gallates of catechin and epicatechin;

the lines at the 2-, 3- and 4-position denote optional R and S configurations;

the lines at the 4- and 8-positions in Formula I and at the 4- and 6- positions in Formula II denote possible oligomer bonds between individual units, and

the substitutions at R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub>, and the configurations at the 2-, 3-, and 4-positions, and the oligomer bond configurations of 4-8 and 4-6 are independently selected for each individual unit and a pharmaceutically acceptable carrier, diluent, or excipient, the therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid,  $\alpha$  -synuclein or NAC fibrillogenesis in a mammalian subject.

29. (Amended) The composition of ~~claim 27~~ claim 28, wherein the therapeutically effective amount of the proanthocyanidin comprises a dosage in the range of about 10 to 1,000 mg/kg of body weight of the subject.

30. (Amended) The composition of ~~claim 29~~ claim 29, wherein the therapeutically effective amount of the proanthocyanidin comprises a dosage in the range of about 10 to 100 mg/kg of body weight of the subject.

31. (Amended) The composition of ~~claim 28~~ claim 29, wherein the proanthocyanidin is selected from the group consisting of ~~chlorogenic acid, epicatechin, epiafzelechin, and the~~ dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable ~~analogues and derivatives~~ salts thereof.

32. (Amended) The composition of ~~claim 31~~ claim 31, wherein the proanthocyanidin is the procyanidin dimer epicatechin-4 $\beta$ →8-epicatechin.

33. (Amended) The composition of ~~claim 31~~ claim 31, wherein the proanthocyanidin is the procyanidin dimer catechin-4 $\alpha$ →8-epicatechin.

34. (Amended) The composition of ~~claim 31~~ claim 31, wherein the proanthocyanidin is the procyanidin dimer epiafzelechin-4 $\beta$ →8-epicatechin.

35. (Amended) The composition of ~~claim 31~~ claim 31, wherein the proanthocyanidin is the procyanidin trimer epicatechin-4 $\beta$ →8-epicatechin-4 $\beta$ →8-epicatechin.

36. (Amended) The composition of claim 31 comprising a mixture of two or more of the proanthocyanidins selected from the group consisting of ~~chlorogenic acid, epicatechin and the~~ dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable ~~analogues and derivatives~~ salts thereof.

37. (Amended) The composition of claim 36 comprising a mixture of two or more of the procyanidins selected from the group consisting of the dimers and trimers of epicatechin, and the pharmaceutically acceptable ~~analogues and derivatives~~ salts thereof.

38. (Previously presented) The composition of claim 36 comprising a mixture of two or more of the proanthocyanidins selected from the group consisting of epicatechin-4 $\beta$ →8-epicatechin, catechin-4 $\alpha$ →8-epicatechin, epiafzelechin-4 $\beta$ →8-epicatechin, and epicatechin-4 $\beta$ →8-epicatechin-4 $\beta$ →8-epicatechin.

39. (Amended) The composition of ~~claim 31~~ claim 31, wherein each proanthocyanidin selected is present in a percentage purity that significantly exceeds a proportion percentage of the proanthocyanidin presence in a plant, or extract from a plant.

40. (Amended) The composition of ~~claim 39~~ claim 39, wherein the proanthocyanidin selected is at least a substantially 70% pure proanthocyanidin.

41. (Amended) The composition of ~~claim 40~~ claim 40, wherein the proanthocyanidin selected is in substantially at least 70% pure isolated or synthetic form.

42. (Withdrawn) A method of isolation of a proanthocyanidin from a plant material containing proanthocyanidins, the method comprising the steps of:

- a) dissolving the plant material with methanol or the like,
- b) then loading the methanol-extracted plant material onto a silica gel column,
- c) eluting the column with a series of increasing proportions of methanol in chloroform to elute the proanthocyanidins,
- d) separating the proanthocyanidins in the extract by reverse phase HPLC, and
- e) collecting and freeze drying the pure proanthocyanidin.

43. (Withdrawn) The method of claim 42 where the series of methanol in chloroform comprises at least 10% methanol in chloroform, 20% methanol in chloroform, 40% methanol in chloroform, 50% methanol in chloroform, and 100% methanol in chloroform.

44. (Withdrawn) A proanthocyanidin composition made from the process of claim 43.

45. (Withdrawn) The composition of claim 44 wherein the proanthocyanidin composition comprises primarily procyanidin dimers and trimers eluted from the silica gel column with the 20% methanol chloroform step of the series.

46. (Withdrawn) The composition of claim 44 wherein the proanthocyanidin composition primarily procyanidin trimers and tetramers eluted from the silica gel column with the 40% methanol in chloroform step of the series.

47. (Withdrawn) The composition of claim 44 wherein the proanthocyanidin composition comprises primarily procyanidin trimers, tetramers, pentamers, and hexamers eluted from the silica gel column with the 50% methanol in chloroform step of the series.

48. (Withdrawn) The composition of claim 44 wherein the proanthocyanidin composition comprises primarily procyanidin tetramers, pentamers, hexamers, and oligomers of greater than six units eluted from the silica gel column with the 100% methanol in chloroform step of the series.

49. (Withdrawn) A method of isolation of a proanthocyanidin from a plant material containing proanthocyanidins, the method comprising the steps of:

- a) dissolving the plant material with ethanol or the like,
- b) then loading the ethanol-extracted plant material onto a LH20 column,
- c) eluting the column with a series of increasing proportions of ethanol, followed by acetone in ethanol and/or methanol to elute the proanthocyanidins,
- d) separating the proanthocyanidins in the extract by reverse phase HPLC, and
- e) collecting and freeze drying the pure proanthocyanidin.

50. (Withdrawn) A method of treatment of an amyloid disease, or a disease characterized by  $\alpha$ -synuclein or NAC fibrillogenesis, in a mammalian subject, the method comprising the step of administering to the subject a therapeutic amount of the proanthocyanidin of claim 44.

51. (Withdrawn) The method of Claim 1 wherein the proanthocyanidin is present in a percentage purity that significantly exceeds a proportion percentage of the proanthocyanidin presence in a plant or extract from the plant.

52. (Withdrawn) The method of claim 11 wherein said amyloid disease for treatment is selected from the group of amyloid diseases associated with Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, inclusion body myositis, the amyloidosis associated with type 2 diabetes, the amyloidosis associated with chronic inflammation, various forms of malignancy, and Familial Mediterranean Fever, the amyloidosis associated with multiple myeloma and other B-cell dyscrasias, the amyloidosis associated with the prion diseases including Creutzfeldt-Jakob disease, Gerstmann-Strausler syndrome, kuru, animal scrapie, and mad cow disease, the amyloidosis associated with long-term hemodialysis and carpal tunnel syndrome, the amyloidosis associated with endocrine tumors

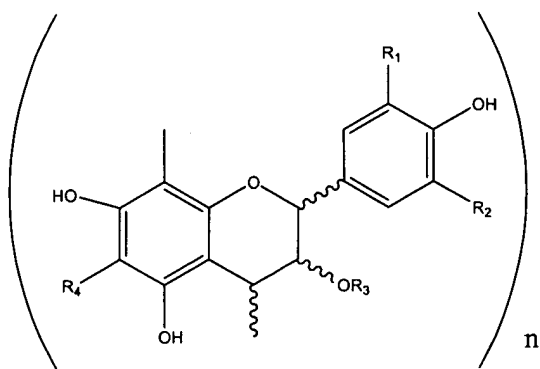


such as medullary carcinoma of the thyroid, and the  $\alpha$ -synuclein/NAC disease is selected from the group consisting of Parkinson's disease, Lewy body disease and multiple system atrophy.

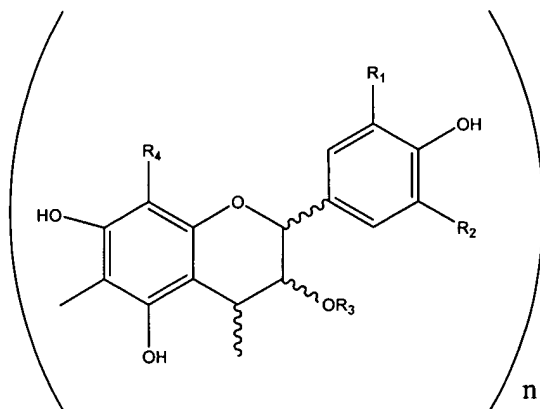
53. (Withdrawn) The method of claim 42 where the plant material is derived from *Uncaria tomentosa*.

54. (Canceled).

55. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of a mixture of substantially at least 70% pure proanthocyanidins, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins:



Formula I



Formula II

where:

n is an integer of 2 to 20;

R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen and hydroxy;

R<sub>3</sub> is selected from the group consisting of hydrogen, optionally substituted O-glycosyl, -C(O)-(optionally substituted aryl), and BC(O)-(optionally substituted heteroaryl);

R<sub>4</sub> is selected from the group consisting of hydrogen, catechin, epicatechin, epiafzelechin, and gallates of catechin and epicatechin;

the lines at the 2-, 3- and 4-position denote optional R and S configurations;

the lines at the 4- and 8-positions in Formula I and at the 4- and 6- positions in Formula II denote possible oligomer bonds between individual units, and

the substitutions at R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub>, and the configurations at the 2-, 3-, and 4-positions, and the oligomer bond configurations of 4-8 and 4-6 are independently selected for each individual unit.

56. (Amended) The composition of ~~claim 55~~ claim 55, wherein one or more of the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable ~~analogues and derivatives~~ salts thereof.